1.0 SCIENTIFIC ABSTRACT

In the year 2000, the estimated incidence of squamous cell cancer of the head and neck (SCCHN) is predicted to be 40,300 cases, and deaths due to SCCHN are predicted to be 11,700. More than two-thirds of the patients with SCCHN present with locally advanced disease, only 30-50% of whom will be cured by surgery, radiation, or combined modality therapy. The most common pattern of failure is loco-regional relapse, with a median survival of six months and a one-year survival of 20%. Despite response rates of 15-31% with single agent chemotherapy, 11-79% with polychemotherapy, 20-40% with radiotherapy or radiochemotherapy, a gain in survival of patients with recurrent disease has yet to be established.

In vitro studies of the early adenoviral gene, E1A, indicate that it acts as a tumor inhibitor by repressing oncogenes, inducing apoptosis, and sensitizing cancer cells to other cancer treatments such as radiation therapy. The E1A gene can be transferred to cells using E1A-Lipid Complex, which consists of the E1A plasmid complexed to the cationic lipid gene delivery system comprised of DC-Cholesterol* and DOPE**. Preclinical animal studies were conducted in a murine model of head and neck cancer. Intratumoral injection of E1A-Lipid Complex resulted in tumor growth inhibition, and extended survival of mice bearing human head and neck WSUHN-31 tumor cells. No meaningful toxicities were seen in mouse toxicology studies performed in support of human clinical trials of E1A-Lipid Complex. The radiosensitizing effects of E1A have been clearly demonstrated in several *in vivo* studies from the literature.

Phase I and II clinical trials of intratumoral injections of E1A-Lipid Complex (1:1) have been performed. In a phase I study (E1A-9602; RAC #9610-162), eighteen patients were enrolled and received E1A-Lipid Complex (1:1) by injection into tumor masses for treatment of metastatic head and neck cancer (nine patients) or metastatic breast cancer (nine patients). Doses ranged from 15-120 μg DNA per cm of maximum tumor diameter. No clinically significant toxicities related to E1A-Lipid Complex were noted. Of 16 evaluable patients, one had a partial response, one had a minor response, nine had stable disease, and five had progressive disease. Biopsies were obtained from seven patients after intratumoral injection; DNA PCR analysis confirmed the presence of the E1A gene.

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* 3β[N', N'-dimethylaminoethane)-carbamoyl] cholesterol

** 1,2-dioleoyl-sn-glycero-3-phosphatidylethanolamine

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In a phase II study (E1A-9801; RAC #9804-246), 24 patients with recurrent head and neck cancer were enrolled and received up to ten intratumoral injections of E1A-Lipid Complex (1:1) at a dose of 30 μg DNA/cm^3 tumor volume per injection. No clinically significant toxicities related to E1A-Lipid Complex (1:1) were noted. Of 21 evaluable patients, one had a complete response, two had minor responses, seven had stable disease, and 11 had progressive disease. E1A gene expression was documented by RT-PCR for mRNA in three of nine evaluable biopsies performed at Day 3.

In this Phase II trial (09B02), up to 50 patients with recurrent squamous cell head and neck cancer despite previous radiotherapy will be treated with twice-weekly intratumoral injections of E1A Lipid Complex (1:1) during re-irradiation. The primary objectives are to determine tumor response by two-dimensional cross-products by CT scan and to evaluate the safety and tolerability of the combination. Secondary objectives include measurement of the time to loco-regional disease progression, and relapse-free and overall survival at one and three years. Immediate and late radiation toxicities will be documented and compared with historical rates to radiation therapy alone